REMARKS

Upon entry of the present amendment, claims 47, 48, 50, 52-84, 86 and 87 will be pending. Applicants have amended claims 47, 48, 50, 53, 60 and 61, and added new claim 87. Claims 1-46, 49, 51, and 68-85 have been canceled without prejudice. Claims 47, 48, 53, 60 and 61 have been amended to point out the claimed subject matter with even ore clarity. Further, support for the amendment to claim 50 can be found, for example, in the disclosure of genes encoding proteins that are localized inside of cells (e.g., non-secreted proteins). See, e.g., Figs. 1-46. Support for new claim 87 can be found throughout the specification, for example, at page 66, lines 16-20; and page 83, lines 16-16. These amendments do not introduce new matter.

35 U.S.C. § 112, Second Paragraph

The Office rejected claim 51 as allegedly being indefinite. Applicants have canceled claim 51 without prejudice or disclaimer, thereby rendering this rejection moot.

35 U.S.C. § 112, First Paragraph

The Office rejected claims 47, 48, 50-67 and 86 as allegedly lacking written description. According to the Office Action (at pages 3 and 4):

> The scope of invention as claimed encompasses any gene expression activity of a CNS sample comprising cell of brain, spinal cord or CSF and other body fluids (where in CNS sample described in the specification as encompassing any bodily fluid samples e.g., serum, blood, lymph, urine, etc see for e.g., specification p.4, lines 29-31 bridging p.5.) of any subject (any animal with bodily fluids) ... Since the specification fails to disclose representative number of species of body fluid tested for a representative number of expressed genes in response to a non-CNS disease it is not possible for one of skill in the art to envision the invention as broadly claimed.

Applicants traverse for the reasons stated below.

First, the present claims do not encompass any body fluids. Rather, the claims require a sample comprising a cell from the brain of the subject, a cell from the spinal cord of the subject, or cerebrospinal fluid (CSF). Applicants note that the previously pending claims also required

that the sample comprise the same cells or fluids, and this did not refer to any body fluid, but have amended the claims to remove the term "CNS sample" to further clarify the invention.

Second, the present specification describes gene expression data obtained with RNA isolated from various regions of the brain (e.g., midbrain, hippocampus, and prefrontal cortex) from mice injected with one of three different kinds of cancer cells (colon carcinoma, lung carcinoma, and breast carcinoma), and from mouse models of asthma and arthritis. See Examples 1-3, 6 and 7. Expression data for a large number of genes for these mouse models of non-CNS diseases were analyzed. See the figures. Further, the specification discloses differentially expressed genes that are predicted or known to encode secreted proteins, and therefore, can be detected in cerebral or spinal fluids. See page 74, lines 3-6; page 75, lines 23-26; page 77, lines 5-8; and page 82, lines 3-6. Thus, the specification provides ample description of a representative number of samples, non-CNS disorders, and genes that can be used in the presently claimed method.

In view of the foregoing, Applicants submit that the present claims are adequately described. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

35 U.S.C. § 102

The Office rejected claims 47, 48, 50-67 and 86 as allegedly anticipated by Petricoin III et al., (The Lancet, 359:572-577, 2002; "Petricoin"). The Office Action states (at page 5):

> Petticoin discloses a method of diagnosing a no-CNS disorder namely ovarian cancer in a subject, the method comprising detecting one or more gene in a CNS-sample (serum), generating gene expression data profile and comparing it with a reference gene expression profile for non-CNS disorder namely ovarian cancer (entire article; abstract) wherein a match of the subjects CNS-sample gene expression is predictive of the subject having or developing said non-CNS disorder. Thus the rejected claims are within the scope of the Petricoin III's disclosure.

Applicants traverse.

As the Office acknowledges, Petricoin describes analyzing serum samples from ovarian cancer patients. The present claims, on the other hand, recite detecting expression of one or

more genes in a sample comprising a cell from the brain of the subject, a cell from the spinal cord of the subject, or cerebrospinal fluid (CSF). Those of ordinary skill in the art would know that the serum from a subject does not contain cells from the brain or the spinal cord, or CSF. Moreover, Petricoin does not disclose analyzing samples containing cells from the brain or the spinal cord, or CSF, and the Office has not pointed to anything in the reference that describes these types of sample.

Thus, Petricoin does not anticipate the present claims. Applicants respectfully request that this rejection under 35 U.S.C. § 102 be reconsidered and withdrawn.

Next, the Office rejected claims 47, 48, 50, 51, and 56-66 as allegedly anticipated by Cleeland et al., (Cancer 97:2919-2925, 2003; "Cleeland"). According to the Office (at page 5 of the Office Action):

> Cleeland further teaches that cytokines may play a mechanistic role in cancer related symptom and teaches a method of diagnosing these effects peripheral cancers by detecting these causative cytokines and the mediators such as ACTH, CRH etc acting downstream from cytokines in brain regions including paraventricular nucleus, hypothalamus and the amygdala (CNS samples) (p.2922; Fig.2). Thus Cleeland's disclosure clearly anticipate the rejected claims.

Again, Applicants traverse.

The Office pointed to Fig. 2 in Cleeland as allegedly describing the presently claimed method. To the contrary, Fig. 2 depicts a schematic representation of "a biologic/physiologic mechanistic framework for cytokine-induced sickness behavior." See the legend for Fig. 2. The legend for Fig. 2 further explains:

> ...proinflammatory cytokines and chemokines ... are released in the periphery by activated immunocytes. They exert their effects on peripheral nerves and directly on the brain to induce various aspects of the sickness response ... The hypothalamic-pituitary-adrenal axis is activated, with up-regulation of the plasma concentration of corticosteroids, which in turn can provide feedback (dotted lines) to limit cytokine production.

In other words, Fig. 2 appears to describe a model for how the release of various cytokines and chemokines and their impact on brain can lead to symptoms seen in cancer patients. Cleeland, as a whole, concerns the role of inflammatory cytokines in cancer symptoms and cancer

treatments. See page 2919 and Fig. 3. There is nothing in Cleeland to even suggest, much less disclose, analyzing the kinds of sample recited in the present claims to diagnose a non-CNS disorder. Neither Fig. 2 nor anything else in Cleeland describes detecting expression of one or more genes in a sample comprising a cell from the brain of the subject, a cell from the spinal cord of the subject, or cerebrospinal fluid (CSF), to determine whether a subject has or will develop a non-CNS disorder.

In view of the foregoing, Applicants submit that Cleeland does not anticipate the present claims. Reconsideration and withdrawal of this rejection under 35 U.S.C. § 102 are respectfully requested.

35 U.S.C. § 103

The Office rejected claims 47, 48, 50-67 and 86 as allegedly obvious over Sridhar et al (W012002124956; "Sridhar") in view of Anderson et al (Molecular & Cellular Proteomics 1 :845-867, 2002; "Anderson"). The Office Action states (at pages 6 and 7):

> ... W0/2002/24956 discloses a method of analyzing CNS samples (as body fluids) and diagnosing several non-CNS disorders, more specifically human tumors as well as analyzing normal human tissue specimens as controls for their gene expression expression [*sic*] profile and diagnosing several non-CNS disorders, more specifically human tumors (entire article; abstract; p.27-28) ...Anderson teaches proteome analytical methods and gene expressing profiling in terms of proteomes in human plasma (a CNS sample) for diagnosing non-CNS disorders including tumors (entire article; abstract; p.861, co1.2 bridging p.862-863).

Applicants traverse for at least the reasons set forth below.

Sridhar discloses analyzing gene expression data obtained from tumor and normal tissues to determine genes that are specific to each tumor and its normal control. See page 27, lines 14-17; and page 28, lines 4-8. According to Sridhar, its invention relates to methods for distinguishing among tumor samples, or between a tumor sample and a normal sample based on the gene expression pattern found in these tumor and normal samples. See page 2, lines 14-25. In other words, Sridhar's methods involve analyzing the gene expression pattern of a sample obtained from a tumor or suspected tumor to determine whether the suspected tumor is actually a tumor and/or to classify the tumor. There is nothing in Sridhar to suggest analyzing a sample

comprising a cell from the brain or the spinal cord, or cerebrospinal fluid (CSF), to determine whether a subject has or will develop a non-CNS disorder. Thus, Sridhar fails to suggest the presently claimed method.

Anderson fails to rectify the deficiencies of Sridhar. As the Office acknowledged, Anderson discloses analyzing the human plasma proteome. Anderson specifically defines plasma to include "all of the protein component of the blood soluble phase (excluding cells)." See pages 845 and 846, the bridging sentence. Thus, aside from the fact that Anderson does not describe analyzing samples containing cells from the brain or the spinal cord, or CSF, the reference actually excludes samples containing cells. Therefore, not only does Anderson fail to suggest the presently claimed method, it would lead those of ordinary skill in the art away from the claimed method. Accordingly, Sridhar and Anderson, alone or in combination, would not have led a person of ordinary skill in the art to the method recited in the present claims.

In view of the above, the current claims are not obvious over Sridhar and Anderson, individually or in combination. Reconsideration and withdrawal of this rejection under 35 U.S.C. § 103 are respectfully requested.

Nonstatutory Obviousness-Type Double Patenting

The Office rejected claims 47, 48, 50-67 and 86 under nonstatutory obviousness-type double patenting as being allegedly unpatentable over claim 47 of Application Serial No. 12/515,314. As it would be more efficient to address this provisional rejection once the scope of allowable subject matter is determined, Applicants defer addressing this rejection until the present claims are found otherwise to be in condition for allowance.

CONCLUSION

Applicants respectfully request that all claims be allowed. Applicants do not concede any positions of the Examiner that are not expressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The extension fee in the amount of $555.00 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 15138-0003US1.

Respectfully submitted,

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